CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-367

CORRESPONDENCE

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 26, 2002

TO: Daniel Shames, M.D., Director
Division of Reproductive and Urologic Drug Products
HFD-580

VIA: Dornette Spell-LeSane, Regulatory Project Manager
Division of Reproductive and Urologic Drug Products
HFD-580

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Regulatory Health Project Manager
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Anne Trontell, M.D., M.P.H., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: DSRCS Review of Patient Labeling for [redacted] (estradiol acetate vaginal ring), NDA 21-367

The patient labeling which follows represents the revised risk communication materials for [redacted] (estradiol acetate vaginal ring) and has been reviewed by our office and by DDMAC. The revisions reflect changes in format, wording, and organization that are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds. Comments are bolded, italicized, and underlined.

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 6 PAGE (S)

Draft

Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jeanine Best
7/26/02 01:13:31 PM
CSO

Anne Trontell
8/1/02 04:59:56 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

Date: July 23, 2002

To: Daniel Shames, M.D.
Acting Director
Division of Reproductive and Endocrine Drug Products

From: Lisa L. Stockbridge, Ph.D.
Regulatory Reviewer
Division of Drug Marketing, Advertising, and Communications
HFD-42

Re: NDA 21-367
Review Prescribing Information and Patient Package Insert for [redacted]
(estradiol acetate vaginal ring) 0.05 mg/day and 0.10 mg/day

Consult Request Date: June 27, 2002
Desired Completion Date: September 1, 2002
Document Date: June 19. 2002
Materials reviewed: [redacted] PI and PPI – version attached to the 6/27/02 consult request

Background:

I have considered the Estring Vaginal Ring and the Premarin PIs in my review for consistency with this new drug product.

PI

Boxed Warning

The second warning in the boxed warning, regarding [redacted] has been omitted from this label. It should be added unless there is a good reason to remove it. If it is decided that it should be removed, then references to it should be removed throughout the PI.

Clinical Pharmacology – Pharmacokinetics subsection

The statement "[redacted] is misleading because it fails take into account the delivery system. If this were true, then Estring (2 mg) should have provided enough estrogen to work for [redacted] This type of claim will be used in advertising. Delete it in the PI if it cannot be substantiated.

Clinical Pharmacology – Metabolism subsection

[redacted]

This is similar to the problem in the Pharmocokinetics subsection, and should be revised or deleted. In addition, there have been several past labels in which we deleted references to the [redacted] because of problems with misleading superiority claims. Thus, it may be wise to delete references to [redacted]

Precautions – General: Expulsion subsection

change [redacted]

Precautions – Pediatric Use subsection

"[

]

This statement should be deleted because there is no substantial evidence that [redacted] may be safe or effective when used in this manner. Similarly, the second and third paragraphs in the Pediatric Use subsection have nothing to do with [redacted] and should be deleted.

Adverse Reactions

The placebo values are missing in my version.

Dosage and Administration

[redacted]

How can you [redacted] this medication?

PPI

There is no standardized PPI for Estring or Premarin at this time. I have examined the proposal by DSRCS and agree with the format and revisions that have been made based on the PI version dated June 27, 2002 (Document Date: June 19, 2002). The final DSRCS version should have incorporated my comments. However, the "What is the most important information I should know about [redacted] section would need modification if the second part of the boxed warning is re-instated.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lisa Stockbridge
7/23/02 01:23:10 PM
CSO

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO: **Office of Postmarketing Drug Assessment (HFD 400)**
Attention: Sammie Beam
Room # 15B23.

FROM: HFD-580 (Division of Reproductive and Urologic Drug Products) Dornette Spell-LeSane, Regulatory Project Manager

DATE:	IND NO.:	NDA NO.:	TYPE OF DOCUMENT:	DATE OF DOCUMENT:
May 10, 2001	[redacted]		request for tradename approval	**May 3, 2001**

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE:
Estradiol vaginal ring	**standard**	**estrogen**	**July 12, 2001**

NAME OF FIRM: **Galen Pharmaceuticals**

REASON FOR REQUEST

I. GENERAL

NEW PROTOCOL
☐ PROGRESS REPORT
☐ NEW CORRESPONDENCE
☐ DRUG ADVERTISING
☐ ADVERSE REACTION REPORT
☐ MANUFACTURING CHANGE/ADDITION
☐ MEETING PLANNED BY

☐ PRE--NDA MEETING
☐ END OF PHASE II MEETING
☐ RESUBMISSION SAFETY/EFFICACY
☐ PAPER NDA
☐ CONTROL SUPPLEMENT

☐ RESPONSE TO DEFICIENCY LETTER
☐ FINAL PRINTED LABELING
☐ LABELING REVISION
☐ ORIGINAL NEW CORRESPONDENCE
☐ FORMULATIVE REVIEW
X OTHER *(SPECIFY BELOW)*:
tradename review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER:	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER:

III. BIOPHARMACEUTICS

☐ DISSOLUTION
☐ BIOAVAILABILTY STUDIES
☐ PHASE IV STUDIES

☐ DEFICIENCY LETTER RESPONSE
☐ PROTOCOL-BIOPHARMACEUTICS
☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ SUMMARY OF ADVERSE EXPERIENCE
☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Sponsor requests tradename review only. No other information available at this time. Sponsor plans to submit NDA July 2001.

cc: Original IND [redacted]
HFD-580/Div. Files
HFD-580/van der Vlugt/Spell-LeSane/ Agarwal/Rumble/Olmstead

SIGNATURE OF REQUESTER:	METHOD OF DELIVERY (Check one): ☐ MAIL HAND
SIGNATURE OF RECEIVER:	SIGNATURE OF DELIVERER:

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/s/

Dornette Spell-LeSane
5/10/01 08:44:02 AM

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ON ORIGINAL

NDA 21-367
estradiol acetate vaginal ring
(0.05 mg/day and 0.1 mg/day
Galen Holdings

Post Marketing Commitments

There are no post-marketing commitments.

GALEN
HOLDINGS PLC

October 15, 2002

Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Fishers Document Room
Room 8B45
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 21-367, estradiol acetate vaginal ring - Amendment No. 15
Proposed Expiry Dating of 24 Months

Dear Sir or Madam:

Based on the currently available stability data, Galen proposes an expiry dating of 24 months for estradiol acetate vaginal rings stored at 20 to 25° C (68 - 77° F).

Please contact the undersigned at (973) 442-3229 if there are any questions stemming from this submission.

Sincerely,

Ileana Brown
Manager
Regulatory Affairs

Enclosures

APPEARS THIS WAY
ON ORIGINAL

GALEN

FAX COVER PAGE

To: **Ms. Dornette Spell-LeSane**
Division of Reproductive and Urologic Drug Products
Fax No. (301) 827-4267 301. 594. 0747

From: Ileana Brown
Manager, Regulatory Affairs
Tel No.: (973) 442-3229
Fax No.: (973) 442-3280

Date: October 15, 2002

Re: NDA 21-367, estradiol acetate vaginal ring
Copy of October 15, 2002 (Amendment 15) Submission

Number of pages including cover page: 2

Dear Ms. Spell-LeSane,

I am providing herein a copy of the submission going out today via FedEx. This submission proposes a 24-month expiry dating based on the currently available stability data.

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

GALEN

FAX COVER PAGE

To: **Ms. Dornette Spell-LeSane**
Division of Reproductive and Urologic Drug Products
Fax No. (301) 827-4267

From: Ileana Brown
Manager, Regulatory Affairs
Tel No.: (973) 442-3229
Fax No.: (973) 442-3280

Date: October 2, 2002

Re: NDA 21-367, estradiol acetate vaginal ring
Table of Hemostatic Parameters for IVR 1006 and Table of STD Testing for IVR 1002

Number of pages including cover page: 12

Dear Ms. Spell-LeSane,

Per your request of this morning, attached are copies of the following tables and their location in the NDA:

Study	Table	Location in NDA	
		Volume	Pages
IVR 1006 Report RR 00901	Table 16.2.14. Hemostatic Parameters	029	22327 - 2333
IVR 1002 Report RR 01101	Listing 22.2. Sexually Transmitted Disease Testing	072*	12439 - 12442

* This listing is also located in Item 10, volume 134, pages 12440 – 12443.

Please let me know if there are any additional questions.

GALEN
OLDINGS PLC

October 1, 2002

Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Fishers Document Room
Room 8B45
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 21-367, estradiol acetate vaginal ring - Amendment No. 13
Correlation Between Hemostasis Parameters and Estradiol Concentrations in Protocols IVR 1005 and IVR 1006

Dear Sir or Madam:

Reference is made to NDA 21-367 for estradiol acetate vaginal ring 0.05 mg/day and 0.10 mg/day submitted on December 21, 2001. Reference is also made to the teleconference of September 13, 2002 during which the correlation between hemostasis parameters and estradiol concentrations was requested for Protocols IVR 1005 and IVR 1006.

Enclosed please find the analysis of each parameter of hemostasis measured in IVR 1005 and IVR 1006 in relation to any observable dependence of these parameters on effects of estradiol; the statistical output as well as the individual listing of parameter values outside of the reference range are included.

Also in this submission are analytical testing documentation pertaining to the seven hemostasis parameters measured and analyzed; the Clinical Pathology Accreditation Certification for Dr. ——— is also provided.

Please contact the undersigned at (973) 442-3229 if there are any questions stemming from this submission.

Sincerely,

Ileana Brown
Manager
Regulatory Affairs

Enclosures

GALEN
HOLDINGS PLC

N-000 BC

ORIGINAL

SEP 2 4 2002
FDR/CDER

September 23, 2002

Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Fishers Document Room
Room 8B45
5600 Fishers Lane
Rockville, Maryland 20857

RECEIVED
SEP 2 4 2002
FDR/CDER

Re: NDA 21-367, estradiol acetate vaginal ring - Amendment No. 12
Response to CMC Information Request

Dear Sir or Madam:

Reference is made to NDA 21-367 for estradiol acetate vaginal ring 0.05 mg/day and 0.10 mg/day submitted on December 21, 2001. Reference is also made to the CMC Information Request dated September 6, 2002. Responses to the Information Request may found in the enclosed volumes (2).

Please contact the undersigned at (973) 442-3229 if there are any questions stemming from this submission.

Sincerely,

APPEARS THIS WAY
ON ORIGINAL

Ileana Brown
Manager
Regulatory Affairs

BEST POSSIBLE COPY

ALEN

LDINGS PLC

DUPLICATE

September 19, 2002

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, Maryland 20852

Re: NDA 21-367, estradiol acetate vaginal ring - Amendment No. 11
Submission of Requested Information Including SAS Dataset

Dear Sir or Madam:

Reference is made to NDA 21-367 for estradiol acetate vaginal ring 0.05 mg/day and 0.10 mg/day submitted on December 21, 2001. Reference is also made to information submitted via facsimile to Ms. Dornette Spell-Lane's attention on September 13, September 16 and September 18, 2002. At this time this information is being submitted to the NDA for archival and may be found in the following pages.

In addition, the data used to generate the table titled 'Analysis of Mean Change From Baseline to Final Evaluation for the Percentage of Parabasal, Intermediate and Superficial Cells' were requested on September 17, 2002. These data, in SAS transport file format, are provided in the enclosed CD. The information was prepared according to the guidance document titled *"Providing Regulatory Submissions in Electronic Format - General Considerations"*, January 1999; virus protection has been ensured with McAfee VirusScan v 4.5.1 software.

Lastly, per the Agency's request a safety update through August 30, 2002 is herein provided.

Please contact the undersigned at (973) 442-3229 if there are any questions stemming from this submission.

Sincerely,

Ileana Brown
Manager
Regulatory Affairs

One CD included

Desk Copy: Ms. Dornette Spell-LeSane

GALEN
OLDINGS PLC

DUPLICATE

September 12, 2002

ORIG AMENDMENT

N-000-BZ

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, Maryland 20852

Re: NDA 21-367, estradiol acetate vaginal ring - Amendment No. 10
Submission of Requested Information Including SAS Dataset

Dear Sir or Madam:

Reference is made to NDA 21-367 for estradiol acetate vaginal ring 0.05 mg/day and 0.10 mg/day submitted on December 21, 2001. Reference is also made to information submitted via facsimile to Ms. Dornette Spell-Lane's attention on August 23, August 30 and September 11, 2002. At this time this information is being submitted to the NDA for archival and may be found in the following pages.

In addition, a dataset requested on September 10, 2002 of the mean vaginal pH and mean change from baseline in vaginal pH in Protocol IVR 1002 is provided in the enclosed CD in SAS transport file format prepared according to the guidance document titled *"Providing Regulatory Submissions in Electronic Format - General Considerations"*, January 1999; virus protection has been ensured with McAfee VirusScan v4.5.1 software.

Please contact the undersigned at (973) 442-3229 if there are any questions stemming from this submission.

Sincerely,

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ON ORIGINAL

Ileana Brown
Manager
Regulatory Affairs

GALEN

FAX COVER PAGE

To: **Ms. Dornette Spell-LeSane**
Division of Reproductive and Urologic Drug Products
Fax No. (301) 827-4267

From: Ileana Brown
Manager, Regulatory Affairs
Tel No.: (973) 442-3229
Fax No.: (973) 442-3280

Date: September 10, 2002

Re: NDA 21-367, estradiol acetate vaginal ring
Letter of Authorization to Cross-Reference ——— DMF

Number of pages including cover page: 2

Dear Ms. Spell-LeSane,

Attached is a letter from ——— authorizing the cross-reference of the DMF for ——— submitted by them on August 30, 2002. The letter will be submitted to NDA 21-367 in the next amendment.

APPEARS THIS WAY
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Courtesy copy
Submitted in
Response

BEST POSSIBLE COPY

[ ]

Food and Drug Administration
Central Document Room
Drug Master File Staff
12229 Wilkins Avenue
Rockville, MD 20852
USA

[ ]

[ ]

August 30, 2002

Our Drug Master File Type II No. "to be assigned" for ———
First submission August 30, 2000

Ladies and Gentlemen,

with this letter in duplicate we authorize the Food and Drug Administration to refer to and incorporate by reference information contained in our Drug Master File and any amendment thereto covering the ——— in any Investigational New Drug Application, New Drug Application or Abbreviated New Drug Application or amendments or supplements thereto filed by

Galen Ltd.
Rockaway 80 Corporate Center
100 Enterprise Drive
Suite 280
Rockaway, New Jersey 07866
USA

The Drug Master File No. "to be assigned" for ——— will be kept current and ——— complies with the statements made in it.

Sincerely yours,

[ ] [ ]

[ ] [ ]

c.c. ———

GALEN

FAX COVER PAGE

To: **Ms. Dornette Spell-LeSane**
Division of Reproductive and Urologic Drug Products
Fax No. (301) 827-4267

From: Ileana Brown
Manager, Regulatory Affairs
Tel No.: (973) 442-3229
Fax No.: (973) 442-3280

Date: August 30, 2002

Re: NDA 21-367, estradiol acetate vaginal ring
Response to Dr. Al-Habet's Request Regarding Age of Rings

Number of pages including cover page: 1

Dear Ms. Spell-LeSane,

On August 28, 2002 you requested on behalf of Dr. Al-Habet the number of patients exposed to rings at 36 months of age. All the studies submitted in the NDA used rings that were no more than 24 months old except for two PK studies (IVR 1001 and IVR 1005) and a non-US, non-pivotal clinical study (HRT 8).

Studies IVR 1001 and IVR 1005 utilized rings retested to extend the expiration date as described respectively in Item 6, Volume 24, page 752 and Volume 30, page 2472 of NDA 21-367 (original application). All patients (n = 12) in IVR 1001 and all patients (n = 14) in IVR 1005 were exposed to rings manufactured at least 36 months before the start of study.

During the time Study HRT 8 was conducted, a [redacted] expiry period was in place. No patients in HRT 8 utilized rings older than 36 months.

The information provided herein will also be submitted as an NDA amendment. Please let me know if further information is required.

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FAX COVER PAGE

To: **Ms. Dornette Spell-LeSane**
Division of Reproductive and Urologic Drug Products
Fax No. (301) 827-4267

From: Ileana Brown
Manager, Regulatory Affairs
Tel No.: (973) 442-3229
Fax No.: (973) 442-3280

Date: August 23, 2002

Re: NDA 21-367, estradiol acetate vaginal ring
Explanation for Table 5, Item 6, Volume 23, Page 270

Number of pages including cover page: 1

Dear Ms. Spell-LeSane,

Per your request of this morning, the following is an explanation of **Table 5. Estradiol Acetate Vaginal Ring Dissolution Test Results for Clinical Study Lots**, found in Item 6, Volume 23, page 270 of NDA 21-367 (original application). The explanation will also be submitted as an NDA amendment. Please let me know if further information is required.

Explanation

Table 5 was prepared to summarize the *in vitro* dissolution data for product studied in clinical trials. The data are tabulated by product strength (column 1), clinical study number (column 2) and product lot number (column 3). Release data was provided for each lot.

Note that over the course of development the ——— and dissolution medium for dissolution method changed from — rpm to rpm and from ——— solution to ——— solution, respectively. Another difference between the test methods was that Day 1 release rate was not determined in the —— method. In cases where the dissolution study for release testing was performed only in ——, available data in —— was also provided. A description of the ——dissolution method is provided in Section 6.4.2 and Table 6 of Item 6.

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JUL 23 2002
HFD-580/CDER

July 19, 2002

ORIG AMENDMENT

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, Maryland 20852

Re: NDA 21-367, [redacted] (estradiol acetate vaginal ring) – Amendment No. 8
Electronic Submission of Proposed Labeling

Dear Sir or Madam:

Reference is made to NDA 21-367 for estradiol acetate vaginal ring submitted on December 21, 2001; the proposed tradename supplied in the NDA was [redacted] which has subsequently changed to [redacted]. Enclosed please find one CD containing two files in MS WORD 2000 for the proposed prescribing information and for the patient information. The same two files are also provided as PDF files (Acrobat Reader 4.0)

Please contact the undersigned at 973.442.3229 if I there are any questions stemming from this submission.

Sincerely,

Ileana Brown
Manager
Regulatory Affairs

Enclosure – one CD

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REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Rockaway 80 Corporate Center ■ 100 Enterprise Drive, Suite 280 ■ Rockaway, New Jersey 07866

ALEN

OLDINGS PLC

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JUL 17 2002

HFD-580/CDER

July 12, 2002

Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Ms. Dornette Spell-LeSane
5600 Fishers Lane
Rockville, Maryland 20857

ORIG AMENDMENT
[/S/]

Re: NDA 21-367, ———— (estradiol acetate vaginal ring)
Proposed Labeling -- DESK COPY

Dear Ms. Spell-LeSane:

Per our conversation on June 11, 2002, enclosed please find one CD containing the proposed prescribing and patient information for estradiol acetate vaginal ring. A CD containing these electronic files saved in MS WORD 2000 was submitted as a desk copy to you on June 18, 2002; unfortunately, opening the files in MS WORD 97 caused format difficulties for tables and figures. At this time the same files saved in MS WORD 97 are submitted in the enclosed CD. These files reflect the proposed prescribing and patient information submitted in the NDA Application except that the proposed name has been changed from ———— to ————.

Thank you for your patience; please contact me if I can offer additional assistance.

Sincerely,

Ileana Brown

Ileana Brown
Manager
Regulatory Affairs

Enclosure – one CD

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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GALEN

HOLDINGS PLC

See Medical Officer's Review [S] 6/26/02

/S/ 7/1/02 rev

ORIGINAL

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JUN 2 0 2002
HFD-580/CDER

June 19, 2002

[/S/]
ORIG AMENDMENT

Ms. Dornette Spell-LeSane
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 21-367, ———— (estradiol acetate vaginal ring) - Amendment No. 7
Submission of Requested Labeling Information

Dear Ms. Spell-LeSane:

Reference is made to the New Drug Application for estradiol acetate vaginal ring, 0.05 mg/day and 0.10 mg/day submitted on December 21, 2001 and to Amendment 6 submitted on May 10, 2002. As indicated on the May 10, 2002 submission, the company is proposing ———— as the proprietary name. Per your request of June 14, 2002, please find the draft professional and patient labeling, and the draft packaging labeling reflecting the new proposed name ———— As you indicated, the information will be forwarded to the Office of Postmarketing Drug Risk Assessment for use in its evaluation of the proposed proprietary name.

Please contact the undersigned at (973) 442-3229 if there are any questions stemming from this submission.

Sincerely,

Ileana Brown

Ileana Brown
Manager
Regulatory Affairs

Enclosure

DESK COPIES (2): Ms. Dornette Spell-LeSane and
Office of Postmarketing Drug Risk Assessment

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ON ORIGINAL

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REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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HOLDINGS PLC

See Medical Officer's Review of NDA /S/ 8/5/02

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MAY 14 2002
HFD-580/CDER

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MAY 13 2002
CDR/CDER

May 10, 2002

/S/
NDA ORIG AMENDMENT

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, Maryland 20852

Re: NDA 21-367, estradiol acetate vaginal ring - Amendment No. 6
Response to INFORMATION REQUEST LETTER of April 19, 2002

Dear Sir or Madam:

Reference is made to the New Drug Application for estradiol acetate vaginal ring, 0.05 mg/day and 0.10 mg/day, submitted on December 21, 2001. Reference is also made to NDA Amendment 3 submitted on April 4, 2002 and to Amendment 5 submitted on April 22, 2002. Amendment 3 provided tables and SAS datasets requested by Ms. Dornette Spell-LeSane via telephone on February 13, 2002. Amendment 5 provided in pdf format two of the files previously included in Amendment 3 per Mr. Randy Levin's request of April 19, 2002 (toc.pdf and contents.pdf).

A letter dated April 19, 2002 has been received listing for the most part the requests made by Ms. Spell-LeSane via telephone on February 13, 2002 and addressed in Amendment 3. Each request in the April 19, 2002 letter is listed below (bold) followed by a response or by a reference to Amendment 3.

1. **Please provide the following:**

   a. **A table showing the mean number of moderate-to-severe vasomotor symptoms (MSVS) at baseline, Week 4, Week 8 and Week 12, the mean change from baseline in the number of MSVS for Week 4, Week 8 and Week 12; and the p-value for Week 4, Week 8 and Week 12 versus placebo for [redacted] 0.05 mg/day and [redacted] 0.10 mg/day using last observation carried forward (LOCF) (ITT population) for Study IVR 1002.**

   b. **A table showing the mean severity of hot flushes at baseline, Week 4, Week 8 and Week 12, the mean change in severity at Week 4, Week 8 and Week 12, and the p-value for Week 4, Week 8 and Week 12 versus placebo for [redacted] 0.05 mg/day and [redacted] 0.10 mg/day using LOCF (ITT) for Study IVR 1002.**

   c. **A table showing the mean percentage of parabasal, intermediate and superficial cells at baseline and Week 12, and the mean change form baseline to Week 12 for placebo, [redacted] 0.05 mg/day, and [redacted] 0.10 mg/day using the ITT population for Study IVR 1002.**

The three tables requested above were provided under the second tab divider in Amendment 3.

ALEN
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HFD-580/CDER

RECEIVED
APR 2 2 2002
CDR/CDER

ORIG AMENDMENT

April 22, 2002

[/S/]

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, Maryland 20852

Re: NDA 21-367, ———— (estradiol acetate vaginal ring) - Amendment No. 5
Partial Re-Submission of Amendment 3

Dear Sir or Madam:

Reference is made to the New Drug Application for ————(estradiol acetate vaginal ring) 0.05 mg/day and 0.10 mg/day submitted on December 21, 2001. On April 4, 2002 Amendment 3 was submitted in response to Ms. Spell-LeSane's request for additional information; the submission included electronic data in one CD.

Mr. Randy Levin telephoned on April 19, 2002 to indicate that two of the files in that CD, namely TOC.TXT and CONTENTS.TXT needed to be re-submitted as pdf files. He further indicated that the SAS datasets included in the CD did not need to be re-submitted. Enclosed please find one CD containing files TOC.PDF and CONTENTS.PDF. Please note that only the archival copy is provided.

Please contact the undersigned at (973) 442-3229 if there are any questions stemming from this submission.

Sincerely,

Ileana Brown
Manager
Regulatory Affairs

Enclosure

REVIEWS COMPLETED
CSO INITIALS
LETTER NAME MEMO
CSO INITIALS DATE

APPEARS THIS WAY
ON ORIGINAL

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Rockaway 80 Corporate Center ■ 100 Enterprise Drive, Suite 280 ■ Rockaway, New Jersey 07866
Phone: (973) 442-3200 Fax: (973) 442-3283 800-521-8813

9 INTRODUCTION

An original New Drug Application for [redacted] (estradiol acetate vaginal ring), NDA 21-367, was submitted to the Division of Reproductive and Urologic Drug Products on December 21, 2001. The submission included an interim (blinded) safety analysis of Study HRT 10, a non-US supportive Phase 3 clinical trial which at the time was ongoing. Although the final study report is under preparation, this four-month safety update provides additional information from the trial as well as from non-US post-marketing experience, and the more recent review of the nonclinical and clinical literature.

The Integrated Summary of Safety (ISS) submitted in the original NDA presented primarily an integrated set of safety data derived from the pivotal study, Study IVR 1002 and from a supportive study, Study HRT 8; safety data from other studies, including Phase 1 studies and Study HRT 10, were presented in the ISS but were not part of the integrated database. Similarly now, preliminary additional safety data from Study HRT 10 are presented without integration.

GALEN
HOLDINGS PLC

ORIGINAL

Noted NAI
For use in MOR
/S/

March 1, 2002

NDA ORIG AMENDMENT

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 21-367, [redacted] (estradiol acetate vaginal ring) - Amendment No. 2
Submission of Requested Information From NDA Filing Meeting

Dear Sir or Madam:

Reference is made to the New Drug Application for [redacted] (estradiol acetate vaginal ring) 0.05 mg/day and 0.10 mg/day submitted on December 21, 2001. Information on the total number of subjects enrolled and discontinued, and total number of protocol violations and serious adverse events in each clinical site participating in the pivotal study (Protocol IVR 1002), was requested by Mr. Roy Blay, Division of Scientific Investigations, on February 11, 2002 and by Ms. Dornette Spell-LeSane, Division of Reproductive and Urologic Drug Products, on February 13, 2002. The tabulated information was sent via facsimile to both individuals on February 19, 2002 and is provided herein for archival.

Please contact the undersigned if there are any questions stemming from this submission.

Sincerely,

Ileana Brown
Manager
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Enclosure

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Rockaway 80 Corporate Center ■ 100 Enterprise Drive, Suite 280 ■ Rockaway, New Jersey 07866
Phone: (973) 442-3200 Fax: (973) 442-3283 800-521-8813

GALEN
HOLDINGS PLC

February 28, 2002

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

NEW CORRESP

Re: NDA 21-367, [redacted] (estradiol acetate vaginal ring) - Amendment No. 1
Request for a Waiver of the Requirement for Pediatric Studies

Dear Sir or Madam:

Reference is made to the New Drug Application for [redacted] (estradiol acetate vaginal ring) 0.05 mg/day and 0.10 mg/day submitted on December 21, 2001. Reference is also made to the Division's letter of January 7, 2002 indicating receipt of the NDA and requesting the submission of documentation in compliance with 21 CFR 314.55. Enclosed please find the request for a waiver of the requirement for pediatric studies. The request was prepared in accordance with the November 2000 draft Guidance to Industry: Recommendations for Complying With the Pediatric Rule (21 CFR 314.55(a) and 601.27(a)).

Please contact the undersigned if there are any questions stemming from this request.

Sincerely,

Ileana Brown

Ileana Brown
Manager
Regulatory Affairs

Enclosure

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Rockaway 80 Corporate Center ■ 100 Enterprise Drive, Suite 280 ■ Rockaway, New Jersey 07866
Phone: (973) 442-3200 Fax: (973) 442-3283 800-521-8813

GALEN
HOLDINGS PLC

ALVIN D. HOWARD
Vice President, Regulatory Affairs

December 19, 2001

Ms. Dornette Spell-LeSane
Division of Reproductive
and Urologic Drug Products (HFD-580)
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 21-367 – [redacted]
IND [redacted] (estradiol acetate [vaginal ring])
Review of Proposed Tradename · [redacted]

Dear Ms. Spell-LeSane:

[redacted] is the proposed tradename for estradiol acetate vaginal ring which is the subject of the New Drug Application (NDA 21-367) being submitted at this time. The indications for [redacted] are treatment of moderate to severe vasomotor symptoms associated with menopause, and [redacted] The proposed tradename was submitted to IND [redacted] on May 3, 2001 (S-019) for preliminary review by the Office of Post-Marketing Drug Risk Assessment; additional information was submitted on August 14, 2001 (S-020).

To assist in the review by the Office of Post-Marketing Drug Risk Assessment, enclosed please find the results of the test conducted for the tradename [redacted] and a copy of the draft labeling including the draft container labeling.

Sincerely,

APPEARS THIS WAY
ON ORIGINAL

Alvin Howard
Vice President
Regulatory Affairs

Enclosure
(2 desk copies)

Rockaway 80 Corporate Center • 100 Enterprise Drive, Suite 280 • Rockaway, New Jersey 07866
Phone: (973) 442-3233• Fax: (973) 442-3280 • e-mail: ahoward@wclabs.com

GALEN
HOLDINGS PLC

ALVIN D. HOWARD
Vice President, Regulatory Affairs

Daniel Shames, M.D., Acting Director
Division of Reproductive and Urologic
Drug Products (HFD-580)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

December 21, 2001

Re: NDA 21-367
Original New Drug Application
[redacted] (estradiol acetate vaginal ring) 0.05 mg/day and 0.10 mg/day

Dear Dr. Shames:

As required by Section 505(b)(1) of the Federal Food, drug and Cosmetic Act, we are herewith submitting for your review and approval a new drug application for [redacted] (estradiol acetate vaginal ring) 0.05 mg/day and 0.10 mg/day.

[redacted] 0.05 mg/day and 0.10 mg/day are indicated for the treatment of moderate to severe vasomotor symptoms associated with menopause, [redacted]

The content and format of this NDA is in accordance with 21 CFR 314.50. Enclosed are a review copy and archival copy of this application. The archival copy of this NDA is comprised of 158 volumes. In accordance with current FDA requirements, a field copy of the chemistry, manufacturing and controls sections is being concurrently submitted to our home FDA district office in North Brunswick, NJ.

Also enclosed under separate cover is market research information in support of our trade name [redacted] This information is being provided to Ms. Dornette Spell Lesane, Regulatory Project Manager, in the Division of Reproductive and Urologic Drug Products.

We trust that the enclosed information is satisfactory. If we can assist you in your evaluation of our application, please do not hesitate to contact me at (973) 442-3233 or Ileana Brown, Manager, Regulatory Affairs at (973) 442-3229.

Sincerely,

Alvin Howard
Vice President
Regulatory Affairs

Rockaway 80 Corporate Center • 100 Enterprise Drive, Suite 280 • Rockaway, New Jersey 07866
Phone: (973) 442-3233• Fax: (973) 442-3280 • e-mail: ahoward@wclabs.com

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-367

Galen Holdings PLC
Attention: Alvin Howard
Vice President, Regulatory Affairs
100 Enterprise Drive
Suite 280
Rockaway, NJ 07866

Dear Mr. Howard:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for [redacted] (estradiol acetate) Vaginal Ring.

We are reviewing various sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. No CMC information pertaining to the manufacture and control of the [redacted] at the [redacted] site has been provided to the NDA. Please comment if additional CMC information will be provided to the NDA to support the manufacture of the [redacted] at the [redacted] site in [redacted]

2. Tables 3, 4 and 5 regarding the accuracy results for the drug substance related substances method are missing from the validation report. Please provide these tables to the NDA.

3. The system suitability parameters used with the [redacted] methods have not been provided with the methods. Please provide the system suitability parameters used in the following methods:
   - Assay of drug substance
   - Related substances in drug substance
   - [redacted] analysis of [redacted]
   - Assay of drug product
   - Related substances in drug product

4. It is recommended that the start of the drug substance retest period begin at the date of manufacture.

5. The proposal in the stability protocols for both drug substance and drug product analyses to redefine time zero if testing is not done within two months is not acceptable. The zero time point should be from the date of manufacture or within a reasonable time after manufacture.

6. Tables 4.2.1 and 4.2.2 (Volume 5, pages 842 – 844) indicate the components and quantitative composition for the proposed theoretical drug product batch of [redacted] rings. Please provide a table to the NDA that will show the actual amounts of the components used in the manufacture of the primary drug product stability batches.

7. Please provide the raw material controls used for the control and analysis of the drug product components, namely [redacted] normal propylorthosilicate, stannous octoate, and barium sulfate.

8. Regarding the 0.050 mg/day and the 0.100 mg/day Drug Product Regulatory Specifications for Release and Stability:

   - Please clarify the use of "for info only" in the regulatory acceptance criteria for total drug assay, content uniformity, and dissolution.
   - We note that in the test for total drug assay, both at release and during stability, for which 10 samples are used to obtain a total drug assay value, that 10 samples is a greater number of samples than typically used for an assay determination. If you prefer to use 10 samples, however, that is acceptable.
   - The acceptance criterion you propose for the total drug assay, that of reporting the mean of 10 analyses, is not acceptable for the following reason. In a 10 sample analysis, if 8 of the 10 rings have individual assay values within [redacted] but 2 of the 10 are outside this range, (for example, one is 80% and the other is 120%) the mean of the 10 analyses will pass the acceptance criterion of mean within [redacted]. This is not acceptable since each individual ring should meet the acceptance criterion. Therefore, we recommend that the acceptance criterion be changed to state that the assay value of each ring tested will be within [redacted] of the expected value.
   - The proposed acceptance criterion for estradiol of NMT [redacted] at release is too high. Based on release data this limit should be set to NMT [redacted] Please change the acceptance criterion for estradiol at release to be NMT [redacted]
   - The proposed acceptance criterion for total related substance of [redacted] is greater than the mean plus three standard deviations of the total amounts tested clinically. Please change the limit to be [redacted]

9. Regarding the 0.050 mcg/day and the 0.100 mcg/day Drug Product In-Vitro Release Regulatory Specification at Release and Stability:

   - Our current thinking regarding in-vitro release testing of reservoir systems such as your drug product is that rings should be tested by a [redacted] protocol. We recommend the following changes to your proposed acceptance criteria:

[redacted]

10. To support the proposed expiry of the drug product, please update the NDA with any additional stability data you have obtained for the drug product primary stability batches. In addition, please include all dissolution data for every ring tested.

11. Please revise your stability protocols to state that during each year the drug substance and drug product are manufactured post-approval, one production batch will be incorporated into the on-going stability program.

12. Please provide a statement that the Medical grade paper to be used for the primary packaging of the drug product (i.e. the pouch) complies with the FDA food packaging requirements.

13. Please provide information on the chemical components of the [redacted] used for the pouch. Additionally, please include the quality specifications for those components.

14. Please provide an update regarding approval of a United States Adopted Name (USAN) for the drug substance.

15. Please submit an Environmental Assessment statement or if eligible a request for a categorical exclusion. Refer to the "Guidance for Industry, Environmental Assessment of Human Drug and Biologics Applications" for additional information.

If you have any questions, call Dornette Spell-LeSane, Regulatory Health Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

David Lin, Ph.D.
Chemistry Team Leader, for the
Division of Reproductive and Urologic Drug Products,
(HFD-580)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

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/s/

David T. Lin
9/6/02 02:45:32 PM
I concur.

APPEARS THIS WAY
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MEETING MINUTES

MEETING DATE: October 10, 2002

TIME: 10:30 am– 11:30 am

LOCATION: PKLN 17B-43

APPLICATION: NDA 21-367

TYPE OF MEETING: 10-month status

SPONSOR: Galen Pharma

DRUG: [redacted] (estradiol acetate) vaginal ring 0.05 mg/day and 0.10 mg/day

MEETING CHAIR: Shelley Slaughter, M.D., Ph.D.

MEETING RECORDER: Dornette Spell-LeSane, NP-C

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Name of FDA Attendee	Title	Division Name & HFD#
1.Shelley Slaughter, M.D., Ph.D.	Medical Team Leader	Division of Reproductive and Urologic Drug Products, DRUDP(H 580)
2.Theresa van der Vlugt, M.D.	Medical Officer	DRUDP (HFD 580)
3.Ameeta Parekh, Ph.D.	Clinical Pharmacology Team Leader	Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUI (HFD-580)
5.Jean Salemme, Ph.D.	Chemist	Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
5.Sayed Al-Habet	Clinical Pharmacology Reviewer	OCPB @ DRUDP (HFD 580)
6.Lynnda Reid, Ph.D.	Pharmacologist	DRUDP (HFD 580)
7.Paul Seligman, M.D.	Office Director	Office of Pharmaceutical Science (HFD 001)
8.Dornette Spell-LeSane	Regulatory Project Manager	DRUDP (HFD 580)

BACKGROUND:
This application was submitted on December 21, 2001. The 10-month PDUFA goal date is October 20, 2002 (Sunday). This product is a vaginal ring containing estradiol acetate intended for 3 months of intravaginal use for treatment of vasomotor symptoms and vulvar and vaginal atrophy.

MEETING OBJECTIVES: To discuss the status of reviews for this application.

DISCUSSION POINTS:

Chemistry:
- Review is with the chemistry Team Leader
- documentation of agreements regarding expiry are pending from sponsor (per t-con October 8, 2002)
- label reviews will be finalized on N drive

Biometrics:
- review is completed (not at meeting)

Clinical Pharmacology:
- briefing conducted October 4, 2002
- information requested from the sponsor as a result of comments from the briefing: evidence of early development data to support establishment of delivery rates (e.g., *invitro* release rates, mean release rates and ranges); sponsor agreed to provide by October 11, 2002
- label comments will be placed on N drive
- copy of review will be forwarded to the medical Team Leader by October 11, 2002
- application is acceptable

Clinical:
- the review is completed
- recommend approval for vulvar and vaginal atrophy and vasomotor symptoms
- sponsor met efficacy for the lower dose for both indications

Pharm-Tox:
- recommend approval
- review will be finalized following confirmation of polymer

Tradename:
- OPDRA will review all of sponsors proposed tradenames; decision expected by October 15, 2002

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ON ORIGINAL

Labeling

- review from the Division of Surveillance, Research, and Communication Support was finalized August 1, 2002; comments are incorporated into medical officers label review
- DDMAC label review was finalized July 23, 2002; comments are incorporated into medical officers label review
- tables in the submitted electronic label are incorrectly formatted; copy of revised tables have been placed on the N-drive as a separate file

ACTION ITEMS:
None

PENDING ITEMS
Tradename review
Overall application recommendation pending Team leader review of final discipline reviews

Minutes Preparer: _____
Dornette Spell-LeSane, Project Manager

Chair Concurrence: _____
Shelley Slaughter, Medical Team Leader

cc: Original
HFD-580/ 21-367/Div. Files
HFD-580/Slaughter, van der Vlugt, Lin, Al-Habet, NG, Salemme

Drafted by: Spell-LeSane, 10.12.02
Initialed by: Salemme, van der Vlugt, 10. 15.02/Slaughter, 10.22.02
final: Spell-LeSane, 11.15.02

MEETING MINUTES

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/s/

Shelley Slaughter
12/13/02 12:46:51 PM
I concur.

APPEARS THIS WAY
ON ORIGINAL

TELECONFERENCE MEETING MINUTES

MEETING DATE: October 8, 2002

TIME: 1:00 pm– 1:30 pm

LOCATION: PKLN 18B-09

APPLICATION: NDA 21-367

TYPE OF MEETING: Guidance

SPONSOR: Galen Pharma

DRUG: [redacted] (estradiol acetate) vaginal ring
0.05 mg/day and 0.10 mg/day

MEETING CHAIR: David Lin, Ph.D.

MEETING RECORDER: Dornette Spell-LeSane, NP-C

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Name of FDA Attendee	Title	Division Name & HFD#
1. David Lin	Chemistry Team leader	Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
2.Jean Salemme	Chemist	DNDC II @ DRUDP
3.Sayed Al-Habet	Clinical Pharmacology Reviewer	Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
4.Dornette Spell-LeSane	Regulatory Project Manager	DRUDP (HFD 580)

SPONSOR ATTENDEES, TITLES, AND COMPANY

Name of sponsor Attendee	Title	Company
1. Alvin Howard	VP of Regulatory Affairs	Galen, US
2.Claire Gillgan, Ph.D., M.R., Pharm.S.	Senior VP, Pharmaceutical Development	Galen
3.Iliana Brown	Manager Regulatory Affairs	Galen, US
4.Grant Elliot, Ph.D.	VP Quality Assurance	Galen
Tina DeVries, PhD	VP Pharmaceutics	Galen

BACKGROUND:
This application was submitted on December 21, 2001. The 10-month PDUFA goal date is October 20, 2002 (Sunday). This product is a vaginal ring containing estradiol acetate intended for 3 months of intravaginal use for treatment of vasomotor symptoms and vulvar and vaginal atrophy. This teleconference was requested by the chemistry and clinical biopharmaceutics review team.

MEETING OBJECTIVES: To request information and discuss the ongoing chemistry and clinical pharmacology reviews for this application.

DISCUSSION POINTS:

Clinical Pharmacology:
- provide or direct to information in the NDA submission, the justification for the delivery rate

Chemistry:
- dissolution is acceptable; numbers for day 1 release will be maintained as proposed
- limit testing range is acceptable
- DRUDP agrees to the amount of estradiol used: no more than [redacted] at release, [redacted] through stability and [redacted] for total related substances and [redacted] during stability
- the stability protocol should be reworded to include a statement regarding a commitment by the sponsor to withdraw lots out of specification during stability testing (see guidance)
- DRUDP does not agree with sentence "limited or restricted testing"; testing should be used that was used during the NDA
- Data does not support [redacted] months expiry; data does support 24 month expiry

AGREEMENTS REACHED:
- sponsor agreed to provide the above requested information for clinical pharmacology
- sponsor agrees to submit written agreement accepting 24-month expiry
- sponsor agrees to submit revised protocol to include requested statements regarding commitments for out of specification stability testing

ACTION ITEMS:
None

Minutes Preparer: _____
Dornette Spell-LeSane, Project Manager

Chair Concurrence: _____
David Lin, Ph.D., Chemistry Team Leader

cc: Original
HFD-580/ 21-367/Div. Files
HFD-580/Slaughter, van der Vlugt, Lin, Al-Habet, Ng, Salemme

Drafted by: Spell-LeSane,
Initialed by: Salemme, 10.15.02/Lin, 12.11.02
final: Spell-LeSane, 12.11.02

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

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/s/

Dornette Spell-LeSane
12/11/02 02:07:23 PM
CSO

Dornette Spell-LeSane
12/11/02 02:09:44 PM
CSO

David T. Lin
12/11/02 04:40:08 PM
CHEMIST
I concur.

APPEARS THIS WAY
ON ORIGINAL

INTERNAL MEETING MINUTES

MEETING DATE: September 12, 2002

TIME: 10:30 am– 11:30 am

LOCATION: PKLN 17B-43

APPLICATION: NDA 21-367

TYPE OF MEETING: 9-month status

SPONSOR: Galen Pharma

DRUG: [redacted] (estradiol acetate) vaginal ring
0.05 mg/day and 0.10 mg/day

MEETING CHAIR: Shelley Slaughter, M.D., Ph.D.

MEETING RECORDER: Dornette Spell-LeSane, NP-C

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Name of FDA Attendee	Title	Division Name & HFD#
1.Shelley Slaughter, M.D., Ph.D.	Medical Team Leader	Division of Reproductive and Urologic Drug Products, DRUDP(H 580)
2.Theresa van der Vlugt, M.D.	Medical Officer	DRUDP (HFD 580)
3.Ameeta Parekh, Ph.D.	Clinical Pharmacology Team Leader	Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRU (HFD-580)
4.David Lin, Ph.D.	Chemistry Team Leader	Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
5.Jean Salemme, Ph.D.	Chemist	DNDC II @ DRUDP (HFD 580)
6.Moh-Jee NG, M.S.	Biometrics Reviewer	DRUDP HFD-580
7.Sayed Al-Habet	Clinical Pharmacology Reviewer	OCPB @ DRUDP (HFD 580)
Lynnda Reid, Ph.D.	Pharmacologist	DRUDP (HFD 580)
8.Dornette Spell-LeSane	Regulatory Project Manager	DRUDP (HFD 580)

BACKGROUND:
This application was submitted on December 21, 2001. The 10-month PDUFA goal date is October 20, 2002 (Sunday). This product is a vaginal ring containing estradiol acetate intended for 3 months of intravaginal use for treatment of vasomotor symptoms and vulvar and vaginal atrophy.

MEETING OBJECTIVES: To discuss the status of reviews for this application.

DISCUSSION POINTS:

Chemistry:
- Manufacturing site inspections went well
- Expiry information being reviewed; sponsor has requested 24 months
- Burst effect increses with the age of the ring
- Information regarding the silicon polymer is under review
- Information request letter was sent September 6, 2002
- USAN information received August 28, 2002

Biometrics:
- review is ongoing

Clinical Pharmacology:
- draft review is completed; however ring age verses estradiol leveles is an issue that is not resolved
- ring age verses estradiol level is an issue; need to determine the clinical effect on the age of the ring; review needs to address the clinical relevance of the age of the ring
- coagulation parameters verses the age of the ring has not been addressed; this is the main issue for CPB review
- request sponsor 1) provide individual data for 17, 29 and 36 month rings for dissolution and 2) data to support coagulation parameters verses age of the ring
- biopharm briefing has not been scheduled; will be scheduled once CPB issues are addressed

Clinical:
- the review is ongoing
- both rings are effective in relief of vasomotor symptoms; both beat placebo;
- for vuvlar and vaginal atrophy; superficial cells do not show a statistical increase in parabasal cells; will review the change in parabasal cells for similar products for comparison
- we will ask the sponsor to provide maturation index on all subjects prior to insertion and transvaginal ultrasound results on individuals without a uterus

Pharm-Tox:
- review is complete with polymer information from chemistry pending
- no carcinogenicity studies will be requested for this application
- label review will review and compare to standard label comments will be applied

Tradename:

- OPDRA will review all of sponsors proposed tradename ——— may not be acceptable; sponsor proposed ——— and ———

Labeling

- Review from the Division of surveillance, Research, and Communication Support
- tables in the submitted electronic label are incorrectly formatted; copy of revised tables will be shared with the reviewers

DSI

- DSI recommended inspection for cause only for 2S applications
- no inspections requested

ACTION ITEMS:
None

PENDING ITEMS
Information request or Discipline review letter

Minutes Preparer: _____
Dornette Spell-LeSane, Project Manager

Chair Concurrence: _____
Shelley Slaughter, Medical Team Leader

APPEARS THIS WAY
ON ORIGINAL

cc: Original
HFD-580/ 21-367/Div. Files
HFD-580/Slaughter, van der Vlugt, Lin, Al-Habet, NG, Salemme, Lin

Drafted by: Spell-LeSane,
Initialed by: Parekh, 10.16.02/Salemme, van der Vlugt, 10.15.02/Slaughter, 10.22.02
final: Spell-LeSane, 11.15.02

MEETING MINUTES

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/s/

Shelley Slaughter
12/13/02 12:43:17 PM
I concur .

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: September 11, 2002

NDA 21-367

BETWEEN:

Name: Ileana Brown, Manager Regulatory Affairs
Phone: 973-442-3229
Representing: Galen Holdings

AND

Name: Dornette Spell-LeSane, Regulatory Project Manager
Division of Reproductive and Urologic Drug Products (HFD-580)

SUBJECT: Clinical and Statistical request for information

1. Prepare a table showing the mean (plus/minus SD) vaginal pH evaluated at baseline and week 13, intent-to-treat population. The submission does contain data by pH range (such as < 4.5, 4.5 to < 5.5, etc) but not the mean pH or the mean change for baseline to week 13. We are unable to locate this information from the datasets submitted.

2. Prepare a table showing the mean percentages of parabasal, intermediate, and superficial cells at baseline and final evaluation; the mean change from baseline to final evaluation for the percentages of parabasal, intermediate, and superficial cells, and the p-value versus placebo for all treated subjects (ITT population with LOCF).

SIGNER'S NAME
TITLE

APPEARS THIS WAY
ON ORIGINAL

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/s/

Dornette Spell-LeSane
9/11/02 12:32:42 PM
CSO

Dornette Spell-LeSane
9/11/02 12:39:10 PM
CSO

APPEARS THIS WAY
ON ORIGINAL

MEETING MINUTES

MEETING DATE: August 8, 2002

TIME: 10:30 am– 11:30 am

LOCATION: PKLN 17B-43

APPLICATION: NDA 21-267

TYPE OF MEETING: 8-month status

SPONSOR: Galen Pharma

DRUG: [redacted] (estradiol acetate) vaginal ring 0.05 mg/day and 0.10 mg/day

MEETING CHAIR: Shelley Slaughter, M.D., Ph.D.

MEETING RECORDER: Dornette Spell-LeSane, NP-C

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Name of FDA Attendee	Title	Division Name & HFD#
1. Shelley Slaughter, M.D., Ph.D.	Medical Team Leader	Division of Reproductive and Urologic Drug Products, DRUDP(H 580)
2. Theresa van der Vlugt, M.D.	Medical Officer	DRUDP (HFD 580)
3. Ameeta Parekh, Ph.D.	Clinical Pharmacology Team Leader	Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUI (HFD-580)
4. David Lin, Ph.D.	Chemistry Team Leader	Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
5. Jean Salemme, Ph.D.	Chemist	DNDC II @ DRUDP (HFD 580)
6. Moh-Jee NG, M.S.	Biometrics Reviewer	DRUDP HFD-580
7. Sayed Al-Habet	Clinical Pharmacology Reviewer	OCPB @ DRUDP (HFD 580)
8. Lynnda Reid, Ph.D.	Pharmacologist	DRUDP (HFD 580)
9. Margaret Kober, R.Ph.	Chief, Regulatory Progect Manager	DRUDP (HFD 580)
10.Dornette Spell-LeSane	Regulatory Project Manager	DRUDP (HFD 580)

BACKGROUND:
This application was submitted on December 21, 2001. The 10-month PDUFA goal date is October 20, 2002 (Sunday). This product is a vaginal ring containing estradiol acetate intended for 3 months of intravaginal use for treatment of vasomotor symptoms and vulvar and vaginal atrophy.

MEETING OBJECTIVES: To discuss the status of reviews for this application.

DISCUSSION POINTS:

Chemistry:
- chemistry review is pending
- information request is pending

Biometrics:
- review of data analysis is ongoing; all requested information has been received
- label review is pending

Clinical Pharmacology:
- review is almost completed
- *in-vivo* aging burst effects of the ring is under review
- sponsor has submitted one-time test at 3 months and line listing for rings in clinical trials used at the beginning of the cycle
- spikes occur at the end of shelf life at — months; *in-vitro* spike data is available for fresh rings; data for aged rings is not available; there is a large spike for *in-vitro* for aging rings; comparisons will have to be determined by analyzing corresponding spikes
- chemistry has information regarding stability data at 6 months, at the end of shelf life that can be reviewed
- reviewer will need to 1) identify spike for end of shelf life and 2) compare *in-vitro* release at 3 months verses 3 weeks

Clinical:
- the review is ongoing

Pharm-Tox:
- review ongoing
- need to confirm from chemist that the — used for the product is the same as that produced by —

Tradename:
- consults sent for revised tradename —

Labeling

- Review from the Division of surveillasnce, Research, and Communication Support
- tables in the submitted electronic label are incorrectly formatted; copy of revised tables will be shared with the reviewers

DSI

- DSI recommended inspection for cause only for 2S applications
- no inspections requested

ACTION ITEMS:
None

PENDING ITEMS
Information request or Discipline review letter

Minutes Preparer: _____
Dornette Spell-LeSane, Project Manager

Chair Concurrence: _____
Shelley Slaughter, Medical Team Leader

APPEARS THIS WAY
ON ORIGINAL

Cc: Original
HFD-580/ 21-367/Div. Files
HFD-580/Slaughter, van der Vlugt, Lin, Al-Habet, NG, Salemme

Drafted by: Spell-LeSane,
Initialed by: Salemme, van der vlugt 10.15.02/Ng, 10.16.02/Slaughter, 10.22.02
Final: Spell-LeSane, 11.15.02

MEETING MINUTES

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Shelley Slaughter
12/13/02 12:53:35 PM
I concur

APPEARS THIS WAY
ON ORIGINAL

INTERNAL MEETING MINUTES

MEETING DATE: June 13, 2002

TIME: 10:30 am– 11:30 am

LOCATION: PKLN 17B-43

APPLICATION: NDA 21-267

TYPE OF MEETING: 6-month status

SPONSOR: Galen Pharma

DRUG: ———— (estradiol acetate) vaginal ring 0.05 mg/day and 0.10 mg/day

MEETING CHAIR: Shelley Slaughter, M.D., Ph.D.

MEETING RECORDER: Dornette Spell-LeSane, NP-C

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Name of FDA Attendee	Title	Division Name & HFD#
1.Shelley Slaughter, M.D., Ph.D.	Medical Team Leader	Division of Reproductive and Urologic Drug Products, DRUDP(H 580)
2.Theresa van der Vlugt, M.D.	Medical Officer	DRUDP (HFD 580)
3.Ameeta Parekh, Ph.D.	Clinical Pharmacology Team Leader	Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUI (HFD-580)
4.David Lin, Ph.D.	Chemistry Team Leader	Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
5.Jean Salemme, Ph.D.	Chemist	DNDC II @ DRUDP (HFD 580)
6.Moh-Jee NG, M.S.	Biometrics Reviewer	DRUDP HFD-580
7.Sayed Al-Habet	Clinical Pharmacology Reviewer	OCPB @ DRUDP (HFD 580)
8.Dornette Spell-LeSane	Regulatory Project Manager	DRUDP (HFD 580)

BACKGROUND:
This application was submitted on December 21, 2001. The 10-month PDUFA goal date is October 20, 2002 (Sunday). This product is a vaginal ring containing estradiol acetate intended for 3 months of intravaginal use for treatment of vasomotor symptoms and vulvar and vaginal atrophy.

MEETING OBJECTIVES: To discuss the status of reviews for this application.

DISCUSSION POINTS:

Chemistry:
- chemistry review is pending
- USAN certification is pending; sponsor should be notified that a pending USAN certification cannot be a phase 4 commitment
- deficiencies should be identified within the next 3 weeks for a information request letter
- manufacturing site inspection is scheduled for the end of July in Ireland; [redacted] chemist will be attending site inspection

Biometrics:
- review of data to determine primary efficacy is in the beginning stages
- second study IVR 1002 has not yet been reviewed
- label review is pending

Clinical Pharmacology:
- review is pending
- no issues identified
- no request for information

Clinical:
- the review is ongoing
- all information requested to date have been received and is being reviewed

Pharm-Tox:
- review ongoing (not present)

Tradename:
- Division of Medication Errors and Technical Support DMETS finds the tradename [redacted] not acceptable
- consults sent for revised tradename [redacted]

Labeling
- consults pending from DMETS and DDMAC

DSI
- DSI recommended inspection for cause only for 2S applications
- no inspections requested

ACTION ITEMS:
None

Minutes Preparer: _____
Dornette Spell-LeSane, Project Manager

Chair Concurrence: _____
Shelley Slaughter, Medical Team Leader

cc: Original
HFD-580/ 21-367/Div. Files
HFD-580/Slaughter, van der Vlugt, Lin, Al-Habet, NG, Salemme

Drafted by: Spell-LeSane,
Initialed by: Salemme, van der Vlugt, 10.15.02, Ng, 11.16.02/Slaughter, 10.22.02
final: Spell-LeSane, 11.15.02

MEETING MINUTES

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Shelley Slaughter
12/13/02 12:50:32 PM
I concur.

APPEARS THIS WAY
ON ORIGINAL

Meeting Minutes

Date: November 7, 2000 **Time**: 2:00 p.m.-3:00 p.m. **Location:** Parklawn; CR-C

IND: IND [redacted] **Drug Name**: estradiol-3-acetate (intravaginal ring)

Indication: Treatment of moderate to severe vasomotor symptoms associated with the menopause
Treatment of vulvar and vaginal atrophy

Sponsor: Galen Limited

Type of Meeting: Pre-NDA

Meeting Chair: Susan Allen

Meeting Recorder: Dornette Spell-LeSane

FDA Participants:
Susan Allen, M.D., M.P.H., Division Director, Division of Reproductive and Urologic Drug Products (DRUDP-HFD-580)
Daniel Shames, M.D., Acting Deputy Director DRUDP (HFD-580)
Shelly Slaughter, M.D., Ph.D., Medical Team Leader, DRUDP (HFD-580)
Theresa van der Vlugt, M.D., MPH., Medical Officer DRUDP (HFD-580)
MooJhong Rhee, Ph.D., Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Michael Ortwerth, Ph.D., Chemist, (DNDC II) @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D., Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) DPE II; (HFD-870) @ DRUDP (HFD-580)
S.W. Johnny Lau, R.Ph., Ph.D., Office of Clinical Pharmacology and Biopharmaceutics @ DRUDP (HFD-580)
Krishan Raheja, D.V.M., Ph.D. - Pharmacologist, DRUDP (HFD-580)
Kate Meaker, M.S. - Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Dornette Spell-LeSane, NP-C, Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:
Norma Enders, R.PH., Vice President, Regulatory Affairs, Warner Chilcott Laboratories
Herman Ellman, M.D., Senior Vice President, Clinical Development, Warner Chilcott Laboratories
Tina de VRIES, Ph.D., Senior Director, Research and Development, Warner Chilcott Laboratories
Claire Gilligan, Ph.D., M.R. Pharm.S., Director, Pharmaceutical Development and Regulatory Affairs, Galen Limited
Clare Passmore, Ph.D., M.P.S.N.I., Director, Scientific Affairs, Galen Limited

Meeting Objective:
To discuss drug development in preparation for an NDA submission.

Background
A Pre-IND meeting was held with this sponsor September 23, 1997, which initiated discussions with the Agency regarding the development of an intravaginal ring (IVR). The sponsor has developed a reservoir-type (IVR) that delivers estradiol-3-acetate (E3A), a pro-drug of estradiol, in a central core which is [redacted] The sponsor is seeking approval for two dosage strengths, a 12.4 mg ring that delivers 0.05 mg estradiol equivalent per day and a 24.8 mg ring that delivers 0.10 mg estradiol equivalent per day. The sponsor plans to submit an NDA in 2001. This meeting has been requested by the sponsor to discuss this application.

Discussion Items:
Specific Questions: **(with answers provided in bolded text)**

Labeling

1. Does the Division agree with the rationale proposed for labeling of the dosage strength?

   The labeling rationale is acceptable with the inclusion of the total amount of E3A in the ring to the label for the E3A-IVR 50 and E3A-IVR 100, 12.4 mg and 24.8 mg, respectively.

CMC Section

1. Does the Division agree that the content and format of the section is appropriate

   The NDA content and format is acceptable with the inclusion of the following: 1) Methods Validation section, 2) Investigational Formulations section, and 3) Drug Product Primary and Secondary Package Labeling information.

2. Is it the opinion of the Division that all of the issues raised at the pre-IND meeting have been covered?

   One issue remains outstanding: the stability studies should include in vitro release rates at [redacted]

3. Does the Division agree that Dow Corning's Silastic® 382 is an appropriate reference material?

   The Dow Corning Silastic® 382 would appear to be an appropriate reference material for the [redacted] elastomer proposed for use in the E3A-IVRs. Full study reports showing equivalency between the Silastic® 382 and the [redacted] elastomer should be submitted to the NDA.

4. Are the drug substance and drug product release specifications appropriate to ensure the identity, purity, potency, and quality of each?

Regarding Drug Substance:

From the data presented at this time, it would appear that the specifications are adequate. A discussion addressing the issue of whether pre-clinical batches have similar impurity profiles should be included in the NDA.

Regarding Drug Product:

a. **For Stress testing, in which the specification is set at [redacted], a quantification of the force used in testing should be included in the NDA.**

b. **For Content Uniformity testing,**
The application of a USP style method for the drug product is recommended.
In detail the following are recommended:

Tier 1 testing:
- **Test 10 rings**
- **Mean value in the range of [redacted]**
- **No more than 1 individual value in the range of [redacted]**

Tier 2 testing:
- **Test an additional 10 rings**
- **Mean value in the range of [redacted]**
- **No more than 2 individual values in the range of [redacted]**
- **No more than 1 individual value in the range of [redacted]**

NOTE: Historical data may be used to propose a similar method with different sampling plans and range values than those given above.

c. **For Dissolution testing,**
- **The range and variance values will be a review issue and will depend on historical data from PK study batches and clinical study batches.**
- **Proposed release and shelf-life dissolution specifications for mean and individual values should be supported by clinical study batches.**
- **Testing is proposed in the meeting package at [redacted] As was previously recommended in the 29-APR-1999 pre-IND meeting, we still recommend time points of [redacted]. The [redacted] testing period proposed does not cover the full prescribing period and may not adequately ensure potency and quality for the drug product.**

NOTE: It may be possible to show that the —— testing plan is adequate. This would require a sufficient body of information to support the equivalency of the —— and —— testing plans.

5. Does the Division agree that the drug substance and finished dosage form stability testing programs, including the specification for each, will fulfill the requirements for submission/approval of the NDA?

Outstanding issues for the sponsor to consider:

- **DRUDP suggest that stability studies should include testing at the intermediate storage condition of 30°C/60%RH.**
- **Stability studies should include in vitro release rates at 1, 9, 45, and 90 days.**

Non-Clinical Section

1. Does the Division agree that the content and format of the section is appropriate?

Yes

2. Does the Division agree that the in vitro and in vivo hydrolysis studies (as described) will support the conclusion that no significant systemic exposure to E3A occurs and, therefore, that no systemic toxicity studies are required for E3A?

This will be a review issue. A discussion regarding the extent of hydrolysis should be provided in the NDA as well as assay limits in determining E3A content.

3. Galen proposes to submit the E3A hydrolysis data in the Non-Clinical Pharmacology and Toxicology section of the NDA only. Please confirm that this is acceptable.

This is acceptable.

4. Does the Division agree with Galen's justification for not carrying out further genotoxicity testing on E3A?

Yes, this may be acceptable pending clinical trial results

5. Does the Division agree with Galen's justification for not carrying out further genotoxicity testing on the elastomer?

Yes, if chemistry review confirms that the compound is similar to the elastomer 382

6. Does the Division agree with the strategy for the presentation of local toxicity data for E3A?

This will depend on clinical and safety data, if no toxicity is evident from the clinical standpoint no further testing will be required

6A. Central to this strategy is the provision of local safety data derived from the E3A-IVR clinical studies in humans, and a consideration of previous human experience with respect to the vaginal administration of estradiol. It is proposed to cross-refer to the Clinical section of the NDA for this data. Is this acceptable?

Yes this is acceptable

6B Galen considers that these (human) data are presented in lieu of local safety data in animals. Does the Division agree?

Yes, this is acceptable.

Human Pharmacokinetic and Bioavailability Section

1. Will the studies described provide sufficient information to characterize both products in accordance with the appropriate requirements of the Human Pharmacokinetics section of the NDA?

Yes, provided the following conditions apply:

- **by "both products" you are referring to the 0.05 E_2 mg/day and 0.1 E_2 mg/day products**
- **the formulation used in the clinical safety and efficacy study is identical to the to-be-marketed formulation (confirmed by the sponsor)**
- **formulation used in Study IVR 1006 (clinical pharmacology) is identical to that for Study IVR 1002 (clinical safety & efficacy); Study IVR 1002 (both 0.05 and 0.1 mg E_2/day products) is sponsor's pivotal clinical safety and efficacy study for indications claim**
- **the formulations used in Study 6a (0.05 [redacted] 0.1 mg E_2/day; dose proportionality) were different from the formulation used in Study 1002**
- **0.1 mg E_2/day formulation information between Studies HRT6a and IVR 1002 to complete the PK data for single dose and dose proportionality could be analyzed by the sponsor**
- **0.1 mg E_2/day formulation in Studies IVR 1001 and HRT 6a are the same but different from that for Study IVR 1002. The sponsor agrees to provide available *in vitro* dissolution and sparse plasma E_2 concentration data from the clinical trial product for bridging the differences found between 0.05 mg and 0.1 mg E_2/day for study 6a and the 0.05 mg and 0.1 mg E_2/day for the clinical trial. This will be a review issue**
- **single and multiple dose PK data for 0.1 mg E_2/day formulation should be provided**

2. Are the methods for calculating the pharmacokinetic parameters acceptable?

- **multiple dose PK data for 0.05 mg E_2/day should be provided**
- **sponsor explained that Study HRT 6a for the 0.1 mg E_2/day is not suitable for C_{max} determination, since early blood sampling were not frequent enough to characterize the initial burst of E3A. Hence Study IVR 1001 was used instead**

- **page 47 of pre-NDA package end of bullet point 4: sponsor confirmed that Study IVR 1006 should be for 0.05 mg E_2/day instead of 0.1 mg E_2/day (typo)**
- **the amount of E3A depleted from the IVR is the difference between the originally assayed E3A and E3A residuals in used IVR; Sponsor described the correction for the lost E3A due to vaginal fluid flow is not needed, since E3A is rapidly absorbed upon release. Another suggested approach to assess the input rate of E_2 would be via the ratio of steady state serum E_2 concentrations to clearance value of E_2. Presentation of results from both approaches in subsequent NDA is recommended**

3. E3A hydrolysis data will be presented in the Non-Clinical Pharmacology and Toxicology Section Should these data also be presented in Item 6 of the NDA?

   E3A hydrolysis data should be presented in Section 6 of the subsequent NDA. Moreover, the bioanalytical assays used in the clinical pharmacology and biopharmaceutics studies for subsequent NDA should be specific for E3A and E_2 and have low cross-reactivity between E3A and E_2, which are demonstrated via bioanalytical assay validation report.

Clinical Section

1. Is the content and structure of Item 8 sufficient to support the efficacy and safety for the two proposed indications?

Yes, this appears appropriate.

2. Are the populations described in the outline analysis plan for the ISS appropriate?

The proposed ISS will incorporate the safety findings from 3 controlled clinical trials: IVR 1002, HRT8 (blinded portion only), HRT 10 (interim safety analysis only), HRT 6, and from 6 PK studies.

3. Is it acceptable to submit a study summary only for HRT 6?

Yes this is acceptable

Case Report Forms

The Case Report Forms (CRFs) for all deaths and discontinuations due to adverse events will be appended to the individual study reports. Is it acceptable to present a tabulation only of these subjects in Item 12 of the NDA?

Yes this is acceptable, electronic submission of CRF's are also acceptable.

Additional Clinical comments:
Sponsor confirms the following:

- in studies HRT 8 and HRT 10 the standard vaginal examination report form used in these clinical studies requires investigator to note presence or absence of epithelial redness, inflammation, ulceration, vaginal discharge or "other"
- all subjects randomized and treated in Study IVR 1002 will undergo a thorough vaginal examination
- all subjects randomized and treated in study IVR 1002 had a physician assessment of vaginal signs and symptoms performed at baseline and end-of-study, not just the colposcopy group
- ratings were used as in HRT 8 and HRT 10 in assessing vaginal changes
- a standard form was developed for completion by the physician in Study IVR 1002 (provided as attachment)

Decisions reached:
Sponsor appears to be adequately prepared for their NDA submission

Action Items:
1. Teleconference with Chemistry reviewer and sponsor may be scheduled, if needed, following review of meeting minutes.
2. A standardized form for vaginal exam requested by the Medical Officer will be provided as an attachment to the meeting minutes.
3. Sponsor should review Guidance document regarding electronic submissions available on the FDA web site.
4. Meeting minutes to be conveyed to Sponsor within 30 days.

APPEARS THIS WAY
ON ORIGINAL

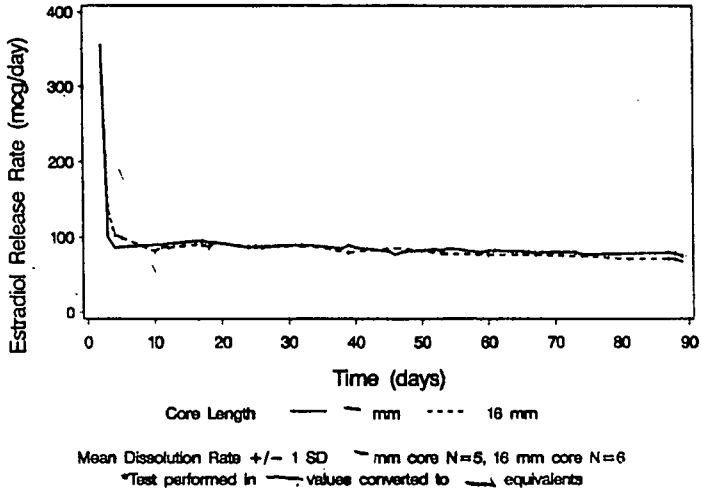
Signature, recorder

Signature, Chair

Attachments:
Summary of Manufacturing Process
Effect of Core Length on In-Vitro Estradiol Release Rate
IVR 1005-Blood estrogen-3-acetate and Serum Estradiol
IVR1005-Percentage Ratio of estrogen-3-acetate to estradiol in vaginal secretion samples after IVR insertion
Vaginal examination Visit 1: Screening
Meeting sign-in sheet

WITHHOLD 1 PAGE (S)

Effect of Core Length on In-Vitro Estradiol Release Rate from E3A-IVR 0.10 mg/day (as estradiol)



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ON ORIGINAL

IVR 1005 - Blood E3A and Serum Estradiol Concentrations

Time	Mean Serum Estradiol Concentration (pg/mL)	Mean E3A Blood Concentration (pg/mL)
0 Min	21.4	ND*
5 Min	182.6	ND
15 Min	896.4	ND
30 Min	1211.3	ND
45 Min	1264.1	ND
60 Min	1280.3	ND
90 Min	1267.8	ND
24 Hr	244.6	ND
72 Hr	104.9	ND

ND = Not Detected (LOD = [redacted]

IVR 1005 - Percentage Ratio of E3A to Estradiol in Vaginal Secretion Samples after IVR Insertion

	90 min		24 hour	
	E3A	Estradiol	E3A	Estradiol
Mean	28.6	71.4	10.5	89.5
Minimum E3A	—	—	—	—
Maximum E3A	—	—	—	—

Screening Number

Assessment Date

	None	Mild	Moderate	Severe	Comments
Atrophy					
Pallor					
Generalised Epithelial Redness					
Discrete Patches of Epithelial Redness					
Inflammation					
Granulation					
Ulceration					
Vaginal Discharge					
Vaginal Dryness					
Friability					
Petechiae					

Investigator Signature_____ Date _____

Wednesday November 7, 2000
Time: 2:00 P.M.
Conference Room-C

Sponsor: Galen Pharmaceuticals
Meeting: Type B
Pre-NDA

NAME/POSITION	ORGANIZATION	SIGNATURE
Susan Allen, M.D., M.P.H., Division Director, Division of Reproductive and Urologic Drug Products (DRUDP HFD-580)	FDA	/S/
Daniel Shames, M.D., Deputy Director, DRUDP (HFD-580)	FDA	/S/
Shelley Slaughter, M.D., Ph.D., Medical Team Leader, DRUDP (HFD-580)	FDA	/S/
Theresa van der Vlugt, M.D., Medical Officer DRUDP (HFD-580)	FDA	/S/
Moo-Jhong Rhee, Ph.D., Team Leader, Division of New Drug Chemistry II, @ DRUDP (HFD-580)	FDA	/S/
Lisa Kammerman, Ph.D., Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)	FDA	
Alexander Jordan, Ph.D., Pharmacology Team Leader, DRUDP (HFD-580)	FDA	
Kate Menker, M.S., Mathematical Statistician, DBII @ DRUDP (HFD-580)	FDA	/S/
Michael Ortwerth, Ph.D., Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)	FDA	/S/
Ameeta Parekh, Ph.D., Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) DPE II; (HFD-870) @ DRUDP (HFD-580)	FDA	/S/
S.W. Johnny Lau, R.Ph., Ph.D., Office of Clinical Pharmacology and Biopharmaceutics @ DRUDP (HFD-580)	FDA	/S/
Krishan Raheja, D.V.M., Ph.D. - Pharmacologist, DRUDP (HFD-580)	FDA	/S/

Wednesday November 7, 2000
Time: 2:00 P.M.
Conference Room-C

Sponsor: Galen Pharmaceuticals
Meeting: Type B
Pre-NDA

NAME/POSITION	ORGANIZATION	SIGNATURE
Terri Rumble, BSN, Chief Project Management Staff, DRUDP (HFD-580)	FDA	
Dornette Spell-LeSane, NP-C, Project Manager, DRUDP (HFD-580)	FDA	/S/
Dr. Claire Gilligan	Galen Limited.	/S/
Dr. Clare Passmore	Galen Limited	/S/
Norma Enders	Warner Chilcott	/S/
Herman Ellman	Warner Chilcott	/S/
—	—	
Tina de Vries	Warner Chilcott	

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND [redacted]

CTS Inc.
Attention: Dr. John A. King, BS.c, Ph.D., MPSN
U.S. Representative, Galen Limited
2661 Audubon Road
Audubon, PA. 19403

Dear Dr. John King:

Please refer to the meeting between representatives of your firm and FDA on November 7, 2000. The purpose of the meeting was to discuss drug development in preparation for an NDA submission.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Dornette Spell-LeSane, NP-C, at (301) 827-4260.

APPEARS THIS WAY
ON ORIGINAL

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Labeling